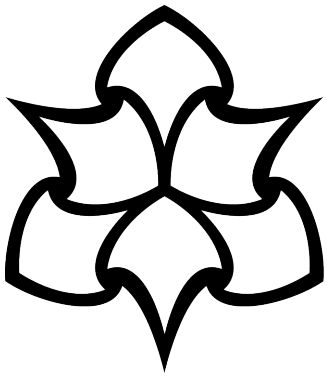

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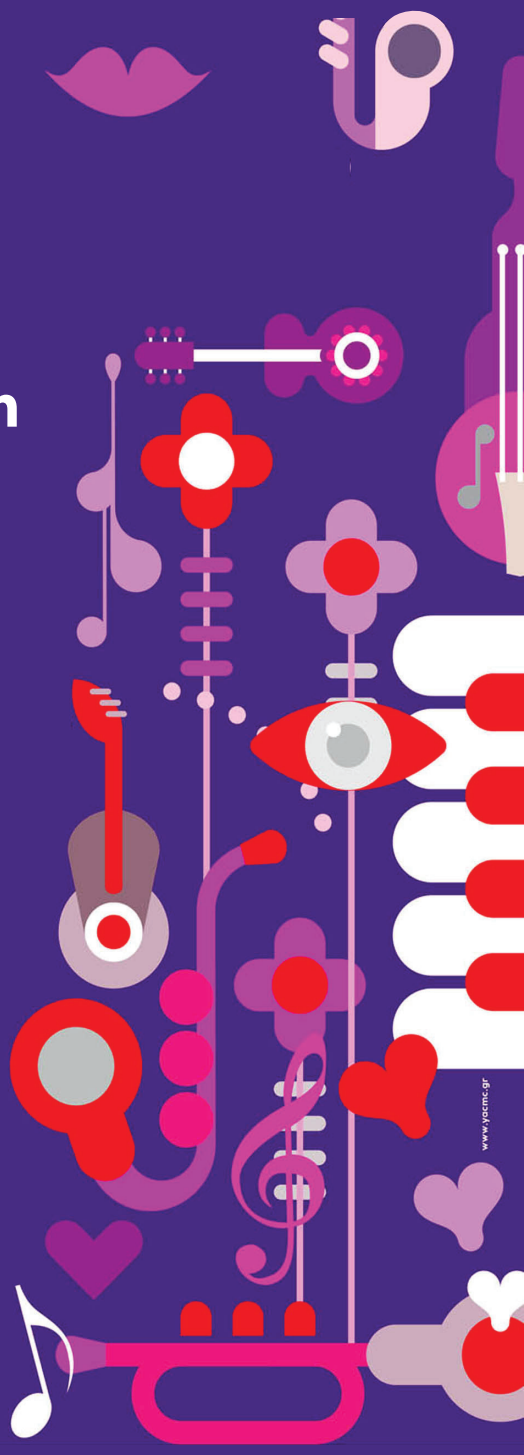

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Contents

Can music listening facilitate reinstating brain dopaminergic activity in substance-addicted individuals? A theoretical review

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Abstract

Substance addiction is one of the most important contemporary medical and social challenges and various pharmacological and psychotherapeutic interventions are currently employed to treat substance addicted individuals. None of them, however, seem to consider reinstating dopaminergic activity in the brain as an important therapeutic target that can prevent relapse and facilitate abstinence. During the last decades, researchers have underscored the necessity to efficiently address this therapeutic goal to enhance therapeutic outcomes. At the same time, a continuously growing amount of evidence seems to indicate that music listening may be a safe non-invasive complementary treatment modality that can enhance the related therapeutic processes by regulating dopamine release in the mesolimbic system and potentially acting as an indirect dopamine agonist. This

review aims to discuss recent research findings about the potential role of music in reinstating brain dopaminergic activity in substance-addicted individuals. The involvement of the mesolimbic dopaminergic pathway in substance addiction will be discussed along with the research findings that showcase the potential capacity of music listening to rehabilitate dopaminergic activity in the brain. Overall, the existing evidence on the potential benefits of music appears to be promising but further experimental research is required to allow the development of interdisciplinary music-assisted therapeutic interventions for reinstating brain dopaminergic activity in substance-addicted individuals.

Keywords: music, substance addiction, dopamine, brain, mesolimbic.

1. Introduction

Substance addiction is considered as one of the most devastating medical and social problems of the last decades. According to previous estimates (UNODC, 2012; WHO, 2014), approximately 3.5 million deaths in 2012 alone were attributed to the harmful use of licit and illicit substances, while substance addiction was implicated in more than 200 disease and injury conditions, as well as in reduced job productivity and increased domestic violence. As a result, substance addiction is now considered as a significant risk factor for social and economic development and prevention policies are continuously being developed at a regional, national and international level to reduce the harmful use of and addiction to substances.

One of the main side-effects of substance addiction is the dysregulated dopaminergic activity in the mesolimbic circuit of the brain (Blum et al., 2008). Current therapeutic practices seem to neglect the importance of this brain function for the proper treatment of substance addiction and for preventing relapse. This has led researchers to underscore the necessity for novel treatment modalities that will address this therapeutic goal during the stages of substance detoxification and rehabilitation, in order to enhance the therapeutic outcomes and sustain abstinence (Blum & Gold, 2011). Of note, a growing amount of evidence has demonstrated that music listening may be a promising non-invasive technique capable

of assisting the respective therapeutic processes (Blood & Zatorre, 2001; Menon & Levitin, 2005). It is, therefore, the aim of this review to provide an overview of the significance of reinstating dopaminergic activity during substance addiction treatment and to critically outline the literature on the potential therapeutic usefulness of music listening as an assisting agent in the process. In light of the existing evidence, it is the authors' hope that this review will contribute to the understanding of the mechanisms by which music can induce a therapeutic effect on the functions of the related brain circuits, and pave the way for future research that will allow the development of interdisciplinary music-assisted therapeutic interventions as complementary treatment modalities for reinstating brain dopaminergic activity during substance addiction treatment.

2. The implication of dopamine in impulsive and compulsive behaviour

Most definitions refer to substance addiction as a phenomenon mainly characterized by compulsive use and the loss of control over substance consumption despite the negative consequences (WHO, 1990). Producing a widely-accepted definition of substance addiction, however, has proven to be a highly complicated issue that seems to have raised great debate on the subject, as evident by the numerous theoretical models that have attempted to explain it and by the confusing interchangeable use of the terms *addiction* and *dependence* (Edwards, 2012). According to Roman law, addiction was defined as the "formal giving over by sentence of court; hence, a dedication of person to a master" (*The Oxford English Dictionary*, 2010), *pp. 24-25*). This definition is conceptually very close to the essence of substance addiction as the central idea is the substance-addicted individuals' relinquishment of control during which the substance becomes the "master" of their behavior while they slowly but steadily dismiss their will power until total submission and loss of control over all aspects of their lives occur. Accordingly, this loss of control - along with the related compulsive use - are currently considered by professionals as the most dominant features of substance addiction (WHO, 1990). Indeed, neurobiological research suggests that addiction represents the transition from impulsive behaviour that is driven by reward-seeking, to compulsive behaviour and substance abuse and addiction. While impulsivity is char-

acterized by a low capacity to control the urge for rewards that influences decision-making during early stages of substance use (Dalley, Everitt, & Robbins, 2011; Verdejo-García, Lawrence, & Clark, 2008), compulsivity is ruled by the lack of control over behaviour and the incapacity to undo response patterns that are no longer associated with reward when addiction develops (Koob & Volkow, 2010). Animal studies have revealed that impulsivity is linked with decreased availability of dopamine receptor D2 in the mesolimbic system of the brain, which, in turn, predicts higher rates of substance use and accelerates the transition to substance addiction, thus emphasizing the importance of genetic makeup in the early stages of substance addiction (Fernandez-Serrano, Perales, Moreno-Lopez, Perez-Garcia, & Verdejo-Garcia, 2012). The notion that dysregulated responsiveness to rewards and the desire for more intense stimulation promote substance-seeking behaviours and addiction (Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010; Goldstein & Volkow, 2002) has also been verified by human studies which showed that substance users who have not yet become addicted present high scores on trait measures of impulsivity and low inhibitory control, which are indicative of modifications in the functions of the striatal system in the brain (Colzato, van den Wildenberg, & Hommel, 2007; Leland, Arce, Feinstein, & Paulus, 2006). In line with this view, dopaminergic activity seems to play an important role in developing habits that lead to compulsive use of substances. More precisely, low levels of D2 dopamine receptor availability in the striatum appear to be associated with deregulation of frontal brain regions linked with inhibitory control and compulsive behaviours which results in loss of control and compulsive substance use at the stage of addiction (Vanderschuren & Everitt, 2005). This process seems to be mediated by high dopamine secretion in response to situations or stimuli related with substance use which leads to repeated actions and learned behaviours of using the substance and eventually results in automatic behavioural responses in the presence of the related stimuli (Volkow et al., 2007).

3. The genetic component of substance addiction

The abuse of and addiction to most addictive substances (True, Xian, et al., 1999; Tsuang et al., 1998) has also been reported to be influenced by genetic components (Kendler, Karkowski, Corey, Prescott, & Neale,

1999; Kendler & Prescott, 1998; Kendler, Prescott, Neale, & Pedersen, 1997; Pickens et al., 1991; True, Heath, et al., 1999; True, Xian, et al., 1999; Tsuang et al., 1996; Uhl, 1999; Uhl, Liu, & Naiman, 2002), such as gene allelic variations and heritable phenotypes (Luo et al., 2004), that promote addiction by contributing to the development of specific personality traits via the interplay with environmental context. In this regard, genes associated with the dopamine system in the brain (Volkow, Fowler, Wang, Swanson, & Telang, 2007) seem to play an important role in the process as they have been found to significantly affect impulsivity and compulsivity and influence substance-seeking behaviours (Kendler, Jacobson, Prescott, & Neale, 2003; Tsuang, Bar, Harley, & Lyons, 2001). Furthermore, individual environmental experiences appear to significantly affect the influence of genetic predisposition on addiction which seems to largely depend on the gene-environment interaction (Kendler et al., 2003). Heritable influences may favour exposure to environments that carry high risk for substance use (Scarr & McCartney, 1983), whereas their expression may be affected by exposure to unsupervised or non-stable environments (Dick et al., 2009; Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001). For instance, studies have shown that one of monozygotic twins that has experienced physical or emotional abuse carries a significantly higher risk to become addicted compared to the twin that has identical genetic profile but has not suffered abuse (Nelson et al., 2006). Additionally, epigenetic alterations are considered to play a major role in the biological aspect of addiction. These gene expression modifications mainly take place in the dopaminergic pathway of the brain that is associated with reward, and are mediated by epigenetic mechanisms, such as histone acetylation and methylation changes (Maze & Nestler, 2011; Renthal & Nestler, 2008). In line with the above notion, a recent view has proposed that future substance use of children may be possible to predict and potentially prevent by assessing hypo-dopaminergic gene expression along with personality and environmental risk factors, highlighting the key role of a healthy dopaminergic system as a preventative action against substance addiction (Conner, Hellemann, Ritchie, & Noble, 2010). This notion is further supported by a genetic study which demonstrated that the A1 allele for the gene coding of dopamine (DA) receptor D2 (*DRD2*) which can be a genetic determinant for hypo-dopaminergic brain function shares a strong link with alcoholism and introduced the first "reward gene" in

the mesolimbic system. Therefore, carriers of this allele are more likely to become addicted to alcohol and potentially to other substances of abuse since common neurobiological facets are shared by different forms of addiction (Blum et al., 1990). It is, therefore, important to gain an in-depth understanding of the dopaminergic circuit functions as this can lead to more advanced and controlled approaches on how to prevent and treat addiction to substances. Such an understanding may allow life-style recommendations to individuals at risk of addiction and enable interventions tailored to individual genetic profiles.

4. The involvement of dopamine in substance-related expectancies

Substance-related expectancies have been shown to be highly implicated in the development of addiction to substances (Christiansen, Smith, Roehling, & Goldman, 1989) as they can become automatic - often unconscious - processes that are responsible for the loss of control and the experience of craving (West, 2005). It has been argued that expectancies are associated with memory structures which control behaviour and may be consciously or unconsciously biased (Field, Mogg, & Bradley, 2004; Franken, Stam, Hendriks, & van den Brink, 2003). The actual loss of control over behaviour is assumed to be mediated by the pre-conscious and pre-attentive processing of the information associated with substance-related cues, which prioritize the stimuli and induce a distinct psychophysiological effect that dominates substance-addicted individuals' awareness, cognitive functions and action tendencies (Ryan, 2002). Of note, expectancies and actions have been found to mutually affect each other (Smith, Goldman, Greenbaum, & Christiansen, 1995), which means that when a substance-addicted individual uses the substance and experiences the expected or desired effect, his expectancies, attentional bias and automatic triggering effect are further enhanced and favour the repetition of the action.

The significance of expectancies has been investigated and verified by research studies which showed that heavy substance use is associated with high levels of positive expectancies and low levels of negative expectancies (Christiansen & Goldman, 1983; Reich, Goldman, & Noll, 2004). Cognitive theorists (Tiffany, 1990) posit that the actual action of substance con-

sumption eventually becomes an automated behavioural response to cues conditioned with substance use, which can induce intense and stressful craving when an addicted individual tries to stop using the substances. Craving responses to substance-related cues are significant risk factors as they favour maintaining substance use during addiction and substance-seeking behaviour during abstinence (Everitt, Dickinson, & Robbins, 2001; van de Laar, Licht, Franken, & Hendriks, 2004). The importance of these responses and of the related cues have been verified by various animal studies (Shaham & Miczek, 2003; Shaham, Shalev, Lu, De Wit, & Stewart, 2003) which showed that conditioned responses persist (Weiss et al., 2001) and often increase in strength (Grimm, Hope, Wise, & Shaham, 2001) even after long periods of abstinence, and that substance-related cues are capable of reinstating negated substance-seeking behaviours (Ciccocioppo, Lin, Martin-Fardon, & Weiss, 2003; Ciccocioppo, Martin-Fardon, & Weiss, 2002; Gracy, Dankiewicz, Weiss, & Koob, 2000). The capacity of environmental stimuli to maintain and reinstate substance-seeking behaviour can be explained by a Pavlovian-based view (LeBlanc, Ostlund, & Maidment, 2012; Ostlund & Balleine, 2008) which argues that substance-induced alterations in the mesolimbic dopaminergic neurotransmission (Saunders, Yager, & Robinson, 2013) increase cue-induced incentive motivation (Ostlund & Maidment, 2012; Wassum, Ostlund, Loewinger, & Maidment, 2013). Interestingly, studies have shown that although substance-addicted individuals exhibit significant DA increases in the mesolimbic system in response to substances, these increases are distinctly blunted compared with controls and considerably lower than the ones induced by substance-associated cues (Volkow, Wang, Fowler, Tomasi, & Telang, 2011). This highlights the contribution of mesolimbic dopaminergic activity in expectations related to the effect of the substances which facilitate maintaining substance use in order to experience the desired effect, and underscore the necessity to include mesolimbic dopaminergic functions as a therapeutic target during substance addiction treatment.

5. The significance of stress as a relapse risk factor and the role of dopamine

Scientific evidence coming from neurobiological studies have highlighted that stress and substance addiction may share common neurobiological facets, and have partly attributed the inability to cope with stress to dysregulated dopaminergic activity (Volkow & Morales, 2015). Consistent with these findings, a wide range of studies have revealed that substance-addicted individuals suffer from both abnormal DA activity (Everitt & Wolf, 2002; Jentsch & Taylor, 1999) and low D2 receptor density (Volkow et al., 2001; Volkow, Wang, Fowler, et al., 1997; Volkow et al., 1996; Wang et al., 2004) in the mesolimbic circuits, which are implicated in the experience of craving (Aujla, Martin-Fardon, & Weiss, 2008; Lu, Uejima, Gray, Bossert, & Shaham, 2007; Sinha, 2008; Weiss, 2005; Zhao et al., 2006). These findings indicate that stress and craving in substance-addicted individuals may share common neurological ground in the brain, which may consequently play an important role in reinstating substance-seeking behaviours and breaking abstinence. Thus, it does not come as a surprise that stress has been identified as a significant relapse risk factor in both human (Kreek & Koob, 1998; Sinha, 2001; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006) and animal studies (Goeders & Guerin, 1994; Mollenauer, Bryson, Robison, Sardo, & Coleman, 1993; Ramsey & Van Ree, 1993) which showed that stress is consistently capable of reinstating substance-seeking behaviour during abstinence (Le & Shaham, 2002; Sarnyai, Shaham, & Heinrichs, 2001; Shalev, Grimm, & Shaham, 2002). Importantly, stress has been associated with craving and relapse (Sinha, Catapano, & O'Malley, 1999; Sinha et al., 2009; Sinha & Li, 2007; Tiffany, 1999) as research findings have revealed that exposure to and experience of stress can evoke intense and long-lasting negative emotion-related cravings (Sinha et al., 2009), potentially due to the perception of substance consumption as the most effective means to alleviate the implicated negative affect (Lazarus & Folkman, 1987; Stathopoulou, 2010). This, in turn, can lead to repeated substance use when experiencing negative emotions or stress and result in automated substance-seeking behaviours in response to stimuli of negative affect which subsequently become cues conditioned with substance use.

6. Mesolimbic dopaminergic neurotransmission and its importance as a therapeutic target

A wide range of studies during the recent decades have provided important evidence on the neurobiological facets of substance addiction. Of importance, it has been demonstrated that hypo-functional dopamine neurotransmission in the mesolimbic pathway of the brain is highly implicated in substance addiction and that slow reinstatement of dopaminergic activity in the aforementioned brain circuit may be necessary for an effective treatment (Gardner, 1999). The dopaminergic pathway is highly involved in feelings of reward, pleasure and euphoria (Melis, Spiga, & Diana, 2005) as well as in pathological behaviours, such as substance addiction. The brain structures involved in its activation are the action sites of most addictive substances, highlighting the complexity and subtlety of this brain section, especially as a therapeutic target (Diana, 2011; Kelly & Berridge, 2002; Stimmel & Kreek, 2000; Volkow, Fowler, Wang, & Goldstein, 2002; Volkow, Wang, Fischman, et al., 1997). The mesolimbic dopaminergic pathway in the brain begins in the Ventral Tegmental Area (VTA) of the midbrain and it is linked by the amygdala, the Nucleus Accumbens (NAc) (Polston, Rubbinaccio, Morra, Sell, & Glick, 2011), the medial prefrontal cortex, and the hippocampus to another set of brain structures known as the limbic system (Schott et al., 2008). The neurotransmitter dopamine is carried via this pathway from one area of the brain to another via signal-transmitting neurons in order to fulfil its biological roles, among which is the control of the brain's pleasure and reward centres; due to this function it has come to be known as the "anti-stress molecule" and/or the "pleasure molecule" (Blood & Zatorre, 2001; Blum et al., 2010). More specifically, in healthy states, dopamine is released by a neuron into the synapse - a structure that permits a neuron to pass a chemical signal to another neuron - where it moves from the pre-synaptic part, into the synaptic cleft (gap between the pre-and post-synaptic neuron) to finally find its target, which are specialised proteins localised at the cell surface of post-synaptic neighbouring nerve cells. These specialised proteins, the dopamine receptors, are activated in response to dopamine binding/docking on them which in turn trigger intracellular signalling in response to this communication. The dopamine is then released from the receptor and along with excess dopamine molecules, that did not bind to an available receptor, it is

pumped back into the presynaptic neuron via the action of a molecule, the dopamine transporter, which is terminating in this way the signal of the neurotransmission and participates in the re-accumulation of dopamine back into the presynaptic cell for future re-use. This well-orchestrated process is disrupted by substances of abuse such as methamphetamines and cocaine that attach to dopamine transporters, thereby blocking dopamine from being taken up back by the presynaptic neuron. Thus, dopamine continues to stimulate the receptors for a longer period resulting in an amplified signal intracellularly producing intense and abnormal euphoria in the user.

The action of dopamine in the brain provides feelings not only of enjoyment but also of reinforcement to motivate a person to perform and repeat certain activities. This notion is present in most theories of addiction as well as in theories of conditioned reinforcement and reward prediction (Blum et al., 2010). In practice, research has shown that elevated levels of DA neurotransmission in the VTA and NAc play a major role in the reinforcing effects of substances of addiction (Robinson & Berridge, 2003). The NAc has shown to be highly involved in the experience of the euphoria induced by psychostimulants like cocaine (Volkow, Wang, Fischman, et al., 1997) and is notably considered to play a major role in the rehabilitation of the dopaminergic system after chronic substance abuse as reactivation of the dopaminergic activity in the brain inevitably involves DA release in the NAc (Blum & Gold, 2011). On the other hand, low DA levels or decreased number of DA receptors is linked with states of anhedonia (inability to experience pleasure), substance-seeking behaviours, relapse, withdrawal symptoms and inability to cope with stress (Koob & Le Moal, 2008; Melis et al., 2005; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Pohjalainen et al., 1998; Wise, 2008).

The above evidence signifies the importance of a balanced dopaminergic activity as a key factor to combat substance addiction. Medical professionals do not seem to agree, however, on how to deal with the issue of deregulated dopaminergic activity during substance addiction treatment. The majority of pharmacological treatments support the administration of opioid receptor agonists and antagonists that block the dopamine release and the subsequent activation of DA receptors (Bowirrat & Oscar-Berman, 2005; Green, Zimmet, Strous, & Schildkraut, 1999; Koob & Le Moal, 2008; Malhotra, Lencz, Correll, & Kane, 2007). Though the former

powerful treatments may have the capacity to decrease the intensity of withdrawal symptoms, they have proved to be inefficient (Koob, Kenneth Lloyd, & Mason, 2009; Leggio et al., 2010; Swift, 2010), present high risk for continued addiction (Dennis et al., 2014) and evoke considerable side-effects (Mizrahi, Houle, Vitcu, Ng, & Wilson, 2010). It becomes evident that both agonist and antagonist treatments do not prioritize reinstating the dopaminergic activity of the brain, neglecting the significance of the regulation of the dopaminergic system during rehabilitation from substance addiction. Of note, deregulated dopaminergic activity exceeds the withdrawal period (Diana et al., 2003; Diana, Pistis, Muntoni, & Gessa, 1996) and poses a great risk factor for relapse (Blum et al., 2009; Diana, Melis, Muntoni, & Gessa, 1998), as reduced DA levels are positively correlated with craving (Lingford-Hughes & Nutt, 2003) and self-drug administration (Blood & Zatorre, 2001; Blum et al., 2008). Furthermore, long periods of low or inhibited dopaminergic activity can result in abnormal mood, depression, anxiety and even suicidal ideation (Blum et al., 2011; Blum & Gold, 2011). On the other hand, controlled moderate DA secretion during the detoxification period may be useful for the alleviation of withdrawal symptoms as not only can it induce feelings of euphoria and pleasure but it can also supress aversive stimuli and emotions (Diana, 2011; Taylor, Joshi, & Uppal, 2003). For these reasons, a growing number of scholars and researchers support the notion that dopaminergic activity in the brain should be slowly but steadily rehabilitated by the use of mild non-pharmacological DA agonists for the proper treatment of substance addiction (Blum et al., 2008; Blum et al., 2011; Blum et al., 2009; Blum et al., 1996; Melis et al., 2005; Rothman, Blough, & Baumann, 2007).

7. The mesolimbic dopaminergic pathway as an emotion-addiction interface

The use of substances is mainly attributed to the emotional effect they elicit (Panksepp, Knutson, & Burgdorf, 2002) which is mediated by dopaminergic neurotransmission in the brain (Everitt & Robbins, 2005; Robinson & Berridge, 2001). As discussed earlier, dopamine is highly associated with the reinforcing effects of substances of abuse (Volkow, Fowler, & Wang, 2004) that are largely responsible for substance use - even when substances cease producing hedonic effects (Berridge & Robinson, 1995;

Robinson & Berridge, 1993, 2003) - and pose a significant risk for relapse (Heinz et al., 2004; Wang et al., 1999). During abstinence, increased DA release in the mesolimbic pathway of the brain in anticipation to the rewarding effects of the substance (Everitt & Wolf, 2002; Jentsch & Taylor, 1999) and decreased DA secretion in response to substance use and natural reinforcers (Aguilar de Arcos, Verdejo-Garcia, Peralta-Ramirez, Sanchez-Barrera, & Perez-Garcia, 2005; Garavan et al., 2000; Martin-Soelch et al., 2001) seem to facilitate substance-seeking behaviours in search of pleasure and rewarding effects (Heinz et al., 2004). Indeed, integral parts of the mesolimbic system, such as the VTA and NAc, become sensitized to the effects elicited by substances of abuse and have been found to be highly implicated in the experience of craving in the presence of stimuli associated with substance use (Lee et al., 2013), as well as in tolerance to substances during the stage of addiction (Berridge, Robinson, & Aldridge, 2009). In reality, the intense feelings of euphoria and pleasure induced by the substances before addiction develops, account for the motivational bias towards repeating the action and later lead to the associative learning that pairs specific endogenous or exogenous cues with substance use. During the later stages of addiction, the neural substrates of VTA and NAc become sensitized in regards to "wanting" (craving) the substance but not to "liking" it (Berridge & Robinson, 1995; Berridge et al., 2009; Volkow & Morales, 2015), which translates into higher release of dopamine in anticipation to the effect of the substance but lower dopamine secretion in response to the substance itself. Consequently, the reduced effect of the substance leads to intense craving, higher doses of the substance and compulsive use, in anticipation of the rewarding effects that will fill or soothe the emotional gap of substance-addicted individuals. Consistent with this view, reduced density of D2 receptors has been found in the striatum of individuals chronically addicted to cocaine, heroin, methamphetamine and alcohol (Volkow et al., 2001; Volkow, Wang, Fowler, et al., 1997; Volkow et al., 1996; Wang et al., 2004), which contributes to biased decision-making that favours substance use. Importantly, low D2 receptor density in the mesolimbic system endures for long periods, even after cessation of substance use (Wang et al., 2004). The latter may be of great significance for relapse prevention as it may affect decision-making during critical parts of therapy. Research findings have further verified that decision-making is affected by neural mechanisms involved in emo-

tion (Bechara, 2004; Bechara, Damasio, & Damasio, 2001; Damasio, 1994; Verdejo-Garcia, Perez-Garcia, & Bechara, 2006) via memory mechanisms that are highly influenced by emotional states and favour the use of substances (Verdejo-Garcia et al., 2006). These findings may partly explain why poor emotional experience and decision-making are common characteristics of substance-addicted individuals (Bechara, 2003, 2004).

8. The effects of music listening on emotion-related brain circuits

Apart from engaging the auditory cortices that are involved in the processing of elementary sound features, such as pitch values and durations (Zatorre & Salimpoor, 2013), pleasant music has been found to induce emotional responses through activation of brain regions implicated in reward, reinforcement, motivation, emotion, approach, withdrawal, arousal, movement, attention, and appraisal (Blood & Zatorre, 2001; Blood, Zatorre, Bermudez & Evans, 1999; Brown, Martinez, & Parsons, 2004; Elliott, Newman, Longe, & William Deakin, 2004; Koelsch, Fritz, V. Cramon, Muller, & Friederici, 2006; Menon & Levitin, 2005; Roitman, Wheeler, & Carelli, 2005; Schultz, 2000; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Tobler, Dickinson, & Schultz, 2003). The main cerebral structures involved in the emotional processing of music with positive emotional valence include circuits of the limbic and paralimbic structures, such as the ventral striatum, amygdala, hippocampus, and insula. The ventral striatum, where dopaminergic neurons project, is highly implicated in reward generation, attention, and motivation (Blood & Zatorre, 2001; Brown et al., 2004; Koelsch et al., 2006; Menon & Levitin, 2005) and has been associated with many forms of positive emotional states (Aharon et al., 2001; Blood & Zatorre, 2001; Brown et al., 2004; Koelsch et al., 2006; Menon & Levitin, 2005; Schultz, 2000). Of note, the VTA and NAc, which are found in the ventral striatum and are highly implicated in the reinforcing effects of substances, present strong activation in response to music (Salimpoor et al., 2011). This activation seems to be mediated by an interaction with cortical networks involved in perceptual analysis and valuation (Salimpoor et al., 2013). The NAc is functionally connected with auditory and frontal areas and their interaction, that results in dopamine release in the NAc, has been positively correlated

with musical reward (Zatorre & Salimpoor, 2013). The capacity of music to regulate dopamine release (Blood & Zatorre, 2001; Menon & Levitin, 2005; Salimpoor et al., 2011) in the striatal dopaminergic system in a manner similar to tangible rewards (Salimpoor et al., 2011) may explain why the music listening experience is so pleasant and leads to feelings of euphoria. However, the positive emotional effect of pleasant music may also be assisted by the suppression of aversive stimuli (Blum et al., 2010) via amygdala deactivation (Blood & Zatorre, 2001), and by stress reduction (Bernatzky, Presch, Anderson, & Panksepp, 2011; Cepeda, Carr, Lau, & Alvarez, 2006) via decreases in cortisol levels (Bartlett, Kaufman, & Smeltekop, 1993; Gerra et al., 1998; Nilsson, 2009; Nilsson, Unosson, & Rawal, 2005). The amygdala is a limbic circuit in the brain that has been found to be associated with negative emotional processing (Phan, Wager, Taylor, & Liberzon, 2002; Zald, 2003) and exhibits strong activation during fearful (Breiter et al., 1996; Morris et al., 1996; Whalen et al., 1998) and sad (Blair, Morris, Frith, Perrett, & Dolan, 1999; Killgore & Yurgelun-Todd, 2004) emotional stimuli. Consequently, amygdala deactivation would essentially be of a rewarding nature (Taylor et al., 2003) since pleasure and pain anchor opposing ends in the spectrum of human emotions (Becerra, Breiter, Wise, Gonzalez, & Borsook, 2001). This notion is consistent with findings which showed that music listening lowers requirements for opiate drugs in postoperative pain (Pecina & Smith, 2010), a process that may well be facilitated by music-induced endogenous opioid-peptide and dopamine release within the brain (Panksepp, 1995). Other studies have verified this hypothesis and showed that chills in response to music listening are attenuated by the opioid receptor antagonist naloxone, providing evidence of a causal link between musical reward and the central release of endogenous opioids (Chanda & Levitin, 2013; A. Goldstein, 1980). Finally, another brain structure that is also activated by pleasant music (Brown et al., 2004) is the hippocampus, a major component of the brain linked with the mesolimbic dopaminergic system and characterised by vulnerability to emotional stressors, induction of tender, positive emotions, affective state regulation, attentional systems, and motivation (Koelsch, 2010; Mega, Cummings, Salloway, & Malloy, 1997; Phillips, Drevets, Rauch, & Lane, 2003). These findings seem to highlight the capacity of music to regulate the activity of brain circuits related with reward, emotion and pleasure.

In regard to musical pleasure itself, studies have shown that it is related to interactions between cortical loops, that give rise to expectancies related to music, and subcortical systems, that modulate reward and valuation (Zatorre & Salimpoor, 2013). The cortical system can decode tonal or rhythmic relationships and produce expectations, while the emotional arousal related to the expectations is mainly induced by interactions with the striatal dopaminergic system (Zatorre & Salimpoor, 2013). A relationship between reward seeking and music was illustrated in a positron emission tomography (PET) scanning study during which listeners were examined on their capacity to release dopamine at different structures of the dopaminergic system (NAc vs caudate) and led authors to conclude that musical pleasure exhibits evidence of an appetitive phase associated with anticipation and a consummatory phase linked with its hedonic and reinforcing effects (Chanda & Levitin, 2013; Salimpoor et al., 2011). Interestingly, the same rewarding process that involves patterns of anatomically and temporally distinct dopaminergic activity in response to music stimuli was reported in animal studies in response to drugs of abuse (Chanda & Levitin, 2013; Volkow et al., 2006). More specifically, in both types of studies, the caudate nucleus, which is highly innervated by dopamine neurons, was more active in anticipation to peak emotional responses either to music or drugs of abuse, while the right NAc, which is also innervated by dopaminergic neurons, exhibited increased activity during the experience of the peaks (Pereira et al., 2011; Salimpoor et al., 2011). These studies indicate that listening to pleasant music and substance use activate the same brain circuits, a finding that could potentially be therapeutically useful for reinstating mesolimbic dopaminergic activity during substance addiction treatment.

9. Music listening for reinstating dopaminergic activity in substance-addicted individuals

As discussed earlier, one of the main negative neurobiological effects of substance addiction is the dysfunction of the dopaminergic activity in the brain, which is implicated in feelings of reward, pleasure and euphoria (Melis et al., 2005) and actively involves brain structures that are the main actions sites of all addictive substances (Diana, 2011; Stimmel & Kreek, 2000; Volkow et al., 2002; Volkow, Wang, Fischman, et al., 1997). During

abstinence, dysfunction in the dopaminergic pathway results in considerably blunted responsiveness to natural rewards (Volkow & Morales, 2015) and consequently to substance-seeking behaviours in search of pleasure. Interestingly, listening to pleasant music is considered as one of the most rewarding experiences capable of evoking intense pleasure and has shown to engage the mesolimbic system circuits involved in reward and emotion that are activated by illicit drugs (Blood & Zatorre, 2001; Blum et al., 2010; Boso, Politi, Barale, & Enzo, 2006; Menon & Levitin, 2005; Salimpoor, Benovoy, Larcher, Dagher & Zatorre, 2011) and to potentiate the related dopaminergic pathway in a manner similar to tangible rewards (Salimpoor et al., 2011; Salimpoor, Benovoy, Longo, Cooperstock & Zatorre, 2009; Salimpoor et al., 2013). In a study conducted by Menon and Levitin (2005), functional magnetic resonance imaging (fMRI) showed that listening to music can modulate the brain mesolimbic activity mainly in the NAc and the VTA, insula and hypothalamus that are implicated in the regulation of the autonomic and physiological reactions during an emotional or rewarding experience. The responses in the NAc and VTA strongly gave rise to the assumption that DA release and NAc response to music are highly associated. Indeed, the study clearly demonstrated that listening to pleasant music resulted in DA release in the VTA and activated the NAc, the VTA, and the hypothalamus. The release of DA can, in turn, activate the dopamine receptors and promote intracellular signalling that can eventually lead to lower levels of stress and heightened feelings of well-being among other physiological functions (Blum et al., 2010). Another related study which used PET scanning, showed that the intensity of pleasure induced by music listening was positively correlated with the ventral striatum activation, that involves dopaminergic activity among other neurotransmitters (Blood & Zatorre, 2001). It can be assumed that positive emotions induced by listening to music may be responsible for activating the NAc and the subsequent secretion of DA (Ashby, Isen, & Turken, 1999) and that the rewarding effect of music may be due to elevated levels of DA in the brain regions of the NAc and the VTA. Indeed, Sutoo and Akiyama (Sutoo & Akiyama, 2004) experimentally demonstrated that elevated brain dopaminergic activity is induced by listening to music and concluded that, by regulating dopaminergic neurotransmission, music may be able to amend the symptoms of conditions associated with DA dysfunction, which is an attractive hypothesis to

be further investigated.

Opioid transmission in the NAc is also linked with DA secretion in the VTA (Kelly & Berridge, 2002). It has been shown that the opioid antagonist naloxone prevents the endorphinergic responses - which control DA release - evoked by music listening (Goldstein, 1980). Schott et al. (2008) demonstrated through fMRI that dopaminergic activity in the brain is quantitatively related to the experience of reward which is mediated by DA release in the mesolimbic system. In that sense, intense reward experiences induced by music may lead to prolonged dopaminergic activation that can be of importance in cases of substance addiction. Furthermore, the sufficient release of DA and activation of the reward circuitry is also dependent on the density of the D2 receptors. Studies have shown that *DRD2* A1 allele carriers, who have lower numbers of D2 receptors and reduced dopamine secretion, present a blunted response to glucose and monetary rewards (Blum et al., 2010). However, this dysfunction can be rescued by bromocriptine, a powerful DRD2 agonist which results in the activation and proliferation of D2 receptors, via DA release (Blum et al., 2010), and consequently to the reduction of craving (Thanos et al., 2001). It is noteworthy that in their study, Blum et al. (2010) concluded that music listening mimicked the effect of bromocriptine. Thus, it is possible to assume that listening to music may have a similar - although slower and less powerful - function to bromocriptine in activating the DA receptors via elevated DA secretion. In other words, listening to music may be possible to act as an indirect D2 agonist by stimulating the biochemical processes responsible for DA release.

An important factor in this process that can be therapeutically exploited appears to be familiarity with music, as it seems to play an important role in the musical enjoyment by increasing the person's liking rates, emotional engagement and the related induction of pleasurable feelings (Pereira et al., 2011). Indeed, it has been shown that dopamine release can occur in response to familiar, highly pleasant music (Salimpoor et al., 2011; Salimpoor et al., 2013) and that this process enhances connectivity between the ventral tegmental area and the NAc, as well as between the NAc and the hypothalamus, indicating familiar and pleasure-related responses in the autonomic nervous system in response to music (Blum et al., 2010; Menon & Levitin, 2005; Sutoo & Akiyama, 2004). Moreover, broad emotion-related limbic and paralimbic brain regions implicated in

the reward circuitry are more active during familiar music when compared to unfamiliar music, thus highlighting the role of familiarity in the emotional engagement to music (Pereira et al., 2011) and its potential therapeutic contribution in the rehabilitation of mesolimbic dopaminergic activity during substance addiction treatment.

10. Music listening may counteract the conditioned psychophysiological effects of substance-related cues

Medical professionals and therapists have emphasized the importance of timely identifying high-risk situations and modifying the implicated behavioural responses that favour substance use (Marlatt, 1985, 1990, 1996). A significant risk factor in this process is the experience of craving as its importance during the phase of treatment has been repeatedly stressed (Franken, 2003). Craving is considered as an emotion (Franken, 2003; Panksepp, 2007) and has been associated with the positive reinforcement of substances (Marlatt, 1985) as well as with the desire to relieve withdrawal symptoms (APA, 2013; Baker, Morse, & Sherman, 1987). Importantly, researchers have highlighted the importance of cues associated with withdrawal or substance use which can induce intense and stressful craving urges when a substance-addicted individual is presented with the related stimuli (Poulous, Hinson, & Siegel, 1981; Tiffany, 1990). These cues result in conditioned psychophysiological and behavioural responses that enhance the motivation for substance use and increase the risk for relapse (Krank & Wall, 1990). Therapeutic approaches, such as cognitive behavioural therapy, primarily aim at extinguishing the impact of the conditioned cues and employ different cue-exposure therapeutic interventions to this end. According to the Positive Psychology theory (Dunn & Dougherty, 2005; Fredrickson, Branigan, & Tugade, 1998; Tugade & Fredrickson, 2004), eliciting positive emotions can counteract the psychophysiological effects induced by negative emotions, such as stress, fear and anxiety. Research studies have verified this hypothesis by showing that cardiovascular arousal induced by fear can be counteracted by evoking positive emotions (Fredrickson et al., 1998; Fredrickson & Levenson, 1998). Since craving is considered as an emotion (Franken, 2003), counterconditioning cues conditioned with substance use would necessitate an alternative emotion-eliciting source that could facilitate modifying and counteract-

ing the conditioned psychophysiological responses related to craving. Of interest, music listening has been proposed as an efficient source for inducing positive emotions (Salimpoor et al., 2011; Salimpoor et al., 2009) that can counteract negative emotional states and psychophysiological symptoms (Allen et al., 2001; Andrade & Bhattacharya, 2003; Hamel, 2001; Phipps, Carroll, & Tsiantoulas, 2010; Schneider, Schedlowski, Schurmeyer, & Becker, 2001; Sutoo & Akiyama, 2004; Thorgaard, Henriksen, Pedersbaek, & Thomsen, 2004; Watkins, 1997), via eliciting a positive effect on the related homeostatic functions (Bernatzky et al., 2011; Sakamoto, Ando, & Tsutou, 2013; Salamon, Kim, Beaulieu, & Stefano, 2003). Neurobiological findings further support this notion as they argue that the capacity of music to induce positive emotions and counteract negative affect is due to dopamine release in the brain's mesolimbic system in response to music (Blood & Zatorre, 2001; Menon & Levitin, 2005; Salimpoor et al., 2011) and to deactivation of the amygdala which is involved in the experience of negative emotions (Blood & Zatorre, 2001; Blood et al., 1999). Aldridge and Fachner (2006) have suggested that this may be the reason that substance-addicted individuals actively listen to music. Furthermore, music listening has shown to counteract negative ideas (Phipps et al., 2010), prevent negative mood (Sarkamo et al., 2008) and enhance positive beliefs that overcome the tendency to counteract them via rational thinking (Salamon et al., 2003). Therefore, it could be argued that listening to pleasant music not associated with substance use may be a useful assisting agent in counterconditioning substance-related cues and in increasing the effectiveness of cue-exposure therapy for substance addiction treatment. Indeed, a pilot study by Stamou et al. (2016, 2017) investigated the effectiveness of music-assisted systematic desensitization for substance addiction treatment and showed that music-assisted cue counterconditioning may be more effective than unreinforced exposure without music. The study also provided evidence of music enhancing the therapeutic effects of systematic desensitization on cognitive and psychopathological components of substance addiction. If these findings are verified by future studies, music-assisted cue exposure may prove to be a useful treatment modality for reacquiring cognitive control over cue reactivity and containing compulsive substance-seeking behaviours during exposure to substance-conditioned cues (Beck, Wright, Newman, & Liese, 1993; Christiansen et al., 1989; Marlatt, 1996).

11. Music listening as a potential relapse risk factor

Apart from its potential therapeutic properties, music has also been associated with substance use and has been identified as a risk factor for relapse (Aldridge & Fachner, 2010). Notably, different music genres have shown to be often matched with different substances in relation to the mood induced by the substance (Aldridge & Fachner, 2006). The repeated substance use accompanied by music has shown to result in music acting as a conditioned cue that may promote relapse (Aldridge & Fachner, 2010; Boening, 2001; Doak, 2003; Esch & Stefano, 2004; Horesh, 2006; Mays, Clark, & Gordon, 2008; White, 1996). Indeed, the aforementioned link between music and substance use has been experimentally verified by animal studies (Polston & Glick, 2011; Polston et al., 2011) which showed that music can act as a conditioned stimulus capable of reinstating substance-seeking behaviours. This association has actually been used by therapists to help substance-addicted individuals attenuate the neurobiological cascade that underlies this effect (Horesh, 2006). Although the above findings indicate the potential risk-carrying properties of music, the notion that music can only act as a cue for substance-seeking behaviours seems to have a narrow perspective. For instance, it would be interesting to see if music could facilitate abstinence by acting as a conditioned stimulus for substance-craving inhibition when paired with a drug or therapeutic modality that attenuates substance-seeking behaviour. Furthermore, research studies have shown that listening to music can modify the level of blood natural opiates (Stefano, Zhu, Cadet, Salamon, & Mantione, 2004) and if future research confirms these findings music listening could serve as a potential substitute for substances during therapy (Aldridge & Fachner, 2010) and facilitate abstinence. This would allow important emotional, physical and social issues (Ghetti, 2004) to be addressed under less pressure during therapy. Indeed, music can provoke a sedative as well as energizing effect and temporarily fill the emotional void experienced during detoxification and early stages of rehabilitation, thus facilitating abstinence before more complicated issued related to substance addiction can be addressed (Aldridge & Fachner, 2006). The capacity of music listening to evoke dopamine release and induce feelings of relaxation, pleasure and euphoria (Blood & Zatorre, 2001; Chanda & Levitin, 2013; Menon & Levitin, 2005; Salimpoor et al., 2011; Volkow et al., 2006) could prove to be beneficial at these stages of treatment. The effect of music

on dopamine-related brain circuits, which may be the reason substance-addicted individuals actively listen to music (Aldridge & Fachner, 2006), could further serve for enhancing engagement to treatment. Additionally, songs are capable of awakening episodic memories (Aldridge & Fachner, 2010; Juslin & Vastfjall, 2008; Juslin & Sloboda, 2001) and could potentially help unbury memories or traumatic events that may be associated with substance addiction and pose a risk for relapse. Music could also assist the development of a trustful relationship between the therapist and the addicted individual and thus, slowly but steadily, facilitate breaking substance-addicted individuals' defences during therapy (Bednarz & Nikkel, 1992). Finally, the link between music and pop culture may also provide an additional therapeutic tool for the exploration and modification of maladaptive emotional and behavioural patterns, for facilitating emotional expression, and for promoting rebuilding of self-identity as a group member in a group therapy setting (Dijkstra & Hakvoort, 2004).

12. Conclusion

The apparent connection between music listening and the dopaminergic-reward pathways in the brain may partly explain why, although not necessary for our survival, music can play an important role in our physical and mental well-being. More importantly, this effect could extend to a significant contribution in the gradual rehabilitation of the dopaminergic activity in the brain of substance-addicted individuals, as evidence shows that music listening has the capacity to regulate DA release and potentially result in the proliferation of D2 receptors. Although one could argue that feelings of pleasure and euphoria may be conditioned with substance use that can lead to substance-seeking behaviours, the existing evidence seems to point to a direction where the careful consideration and use of music listening could have a beneficial effect on dopaminergic activity both during the substance detoxification and rehabilitation stages. The fact that music listening has not been reported to induce serious side-effects and mainly induces pleasurable experiences makes it an attractive solution worth investigating in future experimental studies to allow the development of interdisciplinary music-assisted therapeutic interventions that may act as efficient complementary treatment modalities for re-instating brain dopaminergic activity in substance-addicted individuals.

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